REMARKS

All pending claims have been amended to improve grammar, claims 65 and 66 have been canceled and new claims 71-74 have been added.

Claims 58, 59, 61, 62, 67 and 68 have been amended to recite a "human subject" support for which is found on page 1, lines 13-17 of the Specification and in original claim 1.

Claims 58, 59 and 61 have been amended to recite "effecting presentation" of an immunogenic agent to the immune system; support for which may be found on page 8, lines 10-15 of the Specification.

Claims 58 and 59 have been amended to recite that the immunogenic agent causes an antibody response that cross reacts with said subject's autologous OPGL and thereby down-regulates said autologous OPGL. Support for this amendment is found on page 8, lines 10-25 of the Specification.

Claims 61, 62, 67 and 68 have been amended to recite that that the antibodies of the immune response neutralize autologous OPGL and down-regulate osteoclast differentiation, maturation, formation and activation. Support for this amendment is found on page 8, lines 3-8 of the Specification.

Claims 67 and 68 have been amended to recite administering the claimed antibodies to a human subject suffering from or in danger of suffering from osteoporosis; support for which is found on page 1, lines 13-17 of the Specification.

Claim 69 has been amended to recite that the immunogenic agent is presented to the immune system as a peptide immunogen, a nucleic acid immunogen and/or a non-pathogenic organism. Support for this amendment is found on page 29, lines 22-25, page 36, lines 13-17 and page 39, lines 9-12, respectively, of the Specification.

Support for new claim 71 is found in the Sequence Listing.

Support for new claim 72 is found on page 39, lines 13-17 of the Specification.
Support for new claim 73 is found on pages 33-34 of the Specification.
Support for new claim 74 is found on page 8, lines 10-25 of the Specification.
The claims have been amended to more clearly describe Applicants' invention.
No new matter has been added.

1. Claim Rejections under 35 USC §103/102(e)

The Examiner has maintained her obviousness rejection of the claims over Anderson (U.S. Patent #6,740,522) in view of Tsukii (1998). Applicants respectfully traverse.

Applicants submit that, even when combined, Anderson and Tsukii fail to teach or suggest the presently claimed invention, and the Examiner has failed to establish *a prima facie* case of obviousness. Applicants address the details of the obviousness rejection in the following sections.

1.1 The Anderson Reference

The Examiner accurately states that Anderson teaches RANKL (a.k.a. OPGL) is useful in augmenting an immune response, and is therefore useful as a vaccine adjuvant (column 10, lines 51-62). The Examiner, however, mischaracterizes the Anderson reference as teaching RANKL/OPG L (unmodified with a foreign T-helper epitope) from *any* source species can be used as an immunogen in *any* subject species. In particular, the Examiner broadly and generally states that, as an immunogen, RANKL/OPGL would:

> *...interfere with the action of RANKL/OPGL via antibodies made against the protein in a subject (i.e. down-regulate OPGL).* (Office Action, page 5)

The Examiner seems to view these so-called "teachings" by Anderson as meeting the majority of Applicants' claim elements. This viewpoint, however, is incorrect.

Applicants point out that an "adjuvant" is a molecule that does not induce an immune response directed against itself when presented to an animal's immune system, either alone or in conjunction with another molecule. Rather, an adjuvant causes the immune response mounted against a co-presented molecule to be stronger than it would have been in the absence of the adjuvant. Adjuvants are well-known in the art and defined by Applicants on page 14, lines 20-31 of the Specification.

Anderson teaches autologous RANKL/OPGL is *a general* stimulator of the immune system. Namely, Anderson teaches cell culture assays which show that RANKL/OPGL promotes:

i. Dendritic cell aggregation and fusion (column 24, lines 65-68),
ii. T-cell viability (column 24, lines 51-62),
iii. NF-kB activity (column 19, lines 16-24); and
iv. IL-8 production (columns 19-20, Example 5).

From these cell culture assay results, Anderson extrapolates that autologous RANKL/OPGL would act as a *general* stimulator of the immune system in a human being by virtue of its activities of promoting the above-listed immune functions.

The Anderson extrapolation appears reasonable because RANKL/OPGL is a secreted protein, and it is well known in the art that secreted proteins are generally non-immunogenic when presented to the immune system of an animal of the same species as the animal from which the RANKL/OPGL was derived (*i.e.* in an autologous context). It would seem to follow that administering autologous RANKL/OPGL to an animal would cause an increase in its *in vivo* concentration; and, by mass action principles, stimulate its normal above-listed immune system functions. Applicants submit that Anderson in no way contemplates the possibility that autologous RANKL/OPGL would induce an immune response comprised of antibodies that cross-react with and down-regulate the OPGL of the subject. Here, a well-known analogy would be administering human erythropoietin (a secreted protein) to a human subject, and thereby increasing red blood cell production by mass action (as opposed to inducing an immune response that cross reacts with the subject's erythropoietin and down-regulates red blood cell production).

It is a novel and non-obvious aspect of the present invention to provide a method for down-regulating autologous RANKL/OPGL in a human subject by administering autologous RANKL/OPGL immunogenic agents that induce an immune system response directed against RANKL/OPGL. In no way does Anderson teach this aspect of the presently claimed invention.

In summary, Anderson teaches that autologous RANKL/OPGL is useful as an adjuvant when presented to the immune system of an animal of the same species from which the RANKL/OPGL was obtained. Anderson in no way teaches, as alleged by the Examiner, that autologous RANKL/OPGL would be useful as an immunogen capable of inducing an immune response that is cross-reactive with autologous OPGL, as presently claimed. Anderson therefore fails to teach or suggest the presently claimed invention.

In a second prong of the obviousness rejection, the Examiner contends that Anderson teaches that RANKL/OPGL can be used as an immunogen to generate antibodies (column 22, lines 44-50). In fact, Anderson teaches that mouse antibodies directed against human RANKL/OPGL may be obtained by standard methods (*i.e.* in a heterologous system) (columns 22-23, Example 10). Anderson in no way discloses that injection of autologous RANKL/OPGL into a subject induces an immune response comprising antibodies directed against autologous RANKL/OPGL, as presently claimed.

Based on the foregoing discussion, Applicants submit that an accurate reading of the Anderson patent reveals that it fails to teach the presently claimed methods for down-regulating OPGL activity *in vivo* by presenting to an animal's immune system autologous, immunogenic OPGL.

2.1(b) The Tsukii Reference

The Tsukii reference fails to rescue the deficiencies of Anderson's teachings. In particular, Tsukii teaches the development of rabbit polyclonal antibodies directed against human OPGL by standard methods (once again a heterologous system). In contrast, Applicants claim inducing an immune response comprising antibodies directed against autologous OPGL by presenting autologous OPGL immunogen to a subject's immune system.

Since neither Anderson nor Tsukii teach or suggest methods for down-regulating OPGL activity *in vivo* by presenting to a subject's immune system autologous, immunogenic OPGL, the Examiner has failed to establish *prima facie* obviousness against the presently claimed invention.

2. Claim Rejections under 35 USC §112, First Paragraph - New Matter

The Examiner has rejected claims 67-70 for allegedly containing new matter. The Examiner contends that the Specification fails to provide support for the claim limitation, "to a subject at risk" [for a disease characterized by excessive bone resorption], recited in those claims (Office Action, page 5). Although Applicants do not agree with the Examiner's allegation, Applicants have amended these claims to recite "in danger from suffering from," thereby overcoming the rejection. As indicated above, this limitation has literal support in the Specification (page 1, lines 15-17), and this rejection is thereby obviated.

3. Claim Rejections under 35 USC §112, First Paragraph - Enablement

The Examiner has rejected claims 58-59, 61-62 and 65-70 as allegedly not enabled for":

(a) Claiming a method for "preventing" a disease;
(b) Claiming the use of "any immunogenic agent;"
(c) Claiming the use of "vaccines" (Office Action, pages 6-10).

Applicants respectfully traverse.

3(a) The "Preventing" Enablement Rejection

The Examiner contends that a method for preventing disease is not enabled. Although Applicants do not agree, the claims have been amended to recite methods for treating and ameliorating disease characterized by excessive bone resorption, rather than preventing such disease. Applicants submit that this rejection is thereby overcome.

3(b) The "Immunogenic Agent" Enablement Rejection

The Examiner contends that the use of "an immunogenic agent" to induce an immune response directed against autologous OPGL is not enabled (Office Action, page 6). Applicants respectfully traverse.

By way of overview, the enablement requirement is satisfied when the Specification teaches a person of ordinary skill in the art (POSITA) of the invention how to practice the claimed invention without undue experimentation. Moreover, even where complex experimentation is required to practice an invention, such experimentation is not undue if the art typically engages in such experimentation, the Specification provides direction and guidance regarding the practice of the claimed invention and the skill level of a POSITA is high. In re Wands 858 F.2d at 737, 8 USPQ2d at 1404 and 1406.

Applicants direct the Examiner's attention to pages 42-61 of the instant Specification. There, Applicants provide an extensive description of the kinds of polypeptides, nucleic acids and nonpathogenic microorganisms useful as immunogenic OPGL agents in the presently claimed invention. This disclosure also provides a POSITA with considerable guidance regarding identifying, making and using the claimed OPGL immunogenic agents by way of description, reference to published texts and example. Applicants further point out that general protocols for making and using immunogenic agents are known in the immunology/biotechnology field, and regularly practiced by POSITAs. Here, Applicants call the Examiner's attention to the rich diversity of polyclonal and monoclonal antibodies directed against specific immunogens that are available from both commercial and academic sources. Finally, Applicants submit that the skill level of a POSITA in the immunology/biotechnology field is high, and a POSITA can, due to the teachings of the present Specification and his/her knowledge as a POSITA, skillfully make and use the presently claimed OPGL immunogens with reasonable experimentation.

In view of the foregoing points, Applicants submit that Specification's disclosure in fact provides sufficient guidance for a POSITA to practice the presently claimed invention without undue

experimentation, and the claims are fully enabled. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

3(c) The "Vaccine" Enablement Rejection

The Examiner contends that the administration of a vaccine is not enabled. Again, Applicants do not agree with the Examiner. Yet the claims have been amended to recite the presentation of immunogenic OPGL to the immune system, thereby obviating the rejection.

4. Claim Rejections under 35 USC §112, First Paragraph - Written Description

The Examiner has rejected claims 58-59, 61-62 and 65-70 as allegedly failing to comply with the written description requirement. In particular, the Examiner contends that there is insufficient descriptive support for the claimed immunogenic agent (Office Action, pages 10-11). Applicants respectfully traverse.

Applicants again call the Examiner's attention to pages 42-61 of the instant Specification. There, Applicants provide an extensive description of the kinds of polypeptides, nucleic acids and nonpathogenic microorganisms useful as immunogenic OPGL agents in the presently claimed invention. This disclosure surveys methods for identifying, making and using the claimed OPGL immunogenic agents by express description, reference to published texts and by example. In addition, the Sequence Listing of the present application discloses the exact nucleic acid and amino acid sequences for a substantial number of OPGL immunogens useful in the presently claimed invention.

Applicants submit that this disclosure amounts to a considerable number of OPGL immunogen species in precise structural and physical property terms. Accordingly the Specification indeed conveys to a POSITA that Applicants had possession of the presently claimed OPGL immunogen genus at the time of filing. Applicants have therefore satisfied the written description requirement, and request withdrawal of the rejection.

5. The Double Patenting Claim Rejections

The Examiner has rejected the claims for double patenting (Office Action, page 11). Applicants submit that this rejection will be addressed upon a finding of patentable subject matter.

In view of the foregoing amendments and remarks, Applicants respectfully request allowance of the claims, which are drawn to novel and nonobvious subject matter.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Leonard R. Svensson (Reg. No. 30,330) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), Applicants respectfully petition for a one (1) month extension of time for filing a response in connection with the present application and the required fee should be charged to Deposit Account No. 02-2448.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § § 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,
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